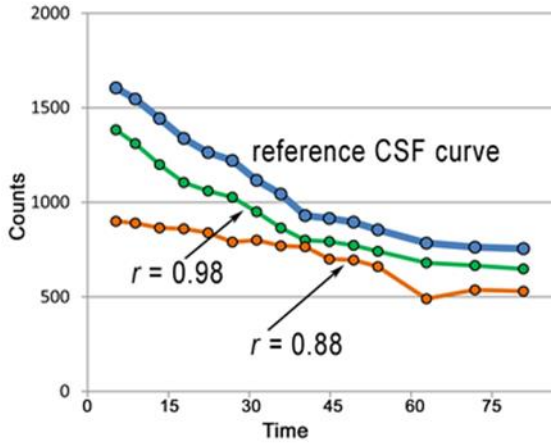
	THK-5117			PiB			
Frame number	duration (sec)	start time (min)	end time (min)	Frame number	scan duration (sec)	start time (min)	end (time)
1	10	0	0.2	1	10	0.0	0.2
2	10	0.2	0.3	2	10	0.2	0.3
3	10	0.3	0.5	3	10	0.3	0.5
4	10	0.5	0.7	4	10	0.5	0.7
5	10	0.7	0.8	5	10	0.7	0.8
6	10	0.8	1	6	10	0.8	1.0
7	10	1	1.2	7	20	1.0	1.3
8	10	1.2	1.3	8	20	1.3	1.7
9	10	1.3	1.5	9	20	1.7	2.0
10	10	1.5	1.7	10	60	2.0	3.0
11	10	1.7	1.8	11	60	3.0	4.0
12	10	1.8	2	12	180	4.0	7.0
13	60	2	3	13	180	7.0	10.0
14	60	3	4	14	300	10.0	15.0
15	120	4	6	15	300	15.0	20.0
16	240	6	10	16	300	20.0	25.0
17	300	10	15	17	300	25.0	30.0
18	300	15	20	18	300	30.0	35.0
19	300	20	25	19	300	35.0	40.0
20	300	25	30	20	300	40.0	45.0
21	300	30	35	21	300	45.0	50.0
22	300	35	40	22	300	50.0	55.0
23	300	40	45	23	300	55.0	60.0
24	300	45	50	24	300	60.0	65.0
25	300	50	55	25	300	65.0	70.0
26	300	55	60				
27	600	60	70				
28	600	70	80				

For each subject, we identified and anatomically mapped CSF positive voxels in the shell region. For every shell voxel (v), a time activity curve (TAC) was correlated (Pearson Product r) with the TAC from the ventricular CSF. The correlations were derived from 14 time points spanning a 3-80 min interval. Formally, , if t_1, t_2, …. t_n are time points in a dynamic PET acquisition, y_i = v (t_i) is the time activity curve of a shell voxel and x_i = CSF (t_i) the time activity curve from CSF, and x and y bar indicate the average value we computed:

$$r = \frac{\sum x_i y_i - n\,\bar{x}\bar{y}}{\sqrt{(\sum x_i^2 - n\bar{x}^2)}\sqrt{(\sum y_i^2 - n\bar{y}^2)}}$$

The figure illustrates this concept on two sample time activity curves. Shell voxels correlated with ventricular CSF with r≥.95 were considered CSF positive.



Supplemental Fig.1. Schematic comparison of TAC curves. The figure shows a reference TAC for CSF (blue) and TAC for two sample shell voxels: green = voxel highly correlated with CSF, *r* = .98; and orange curve shows lower correlation *r* = .88. The correlations were based on the 3-80min time frames.

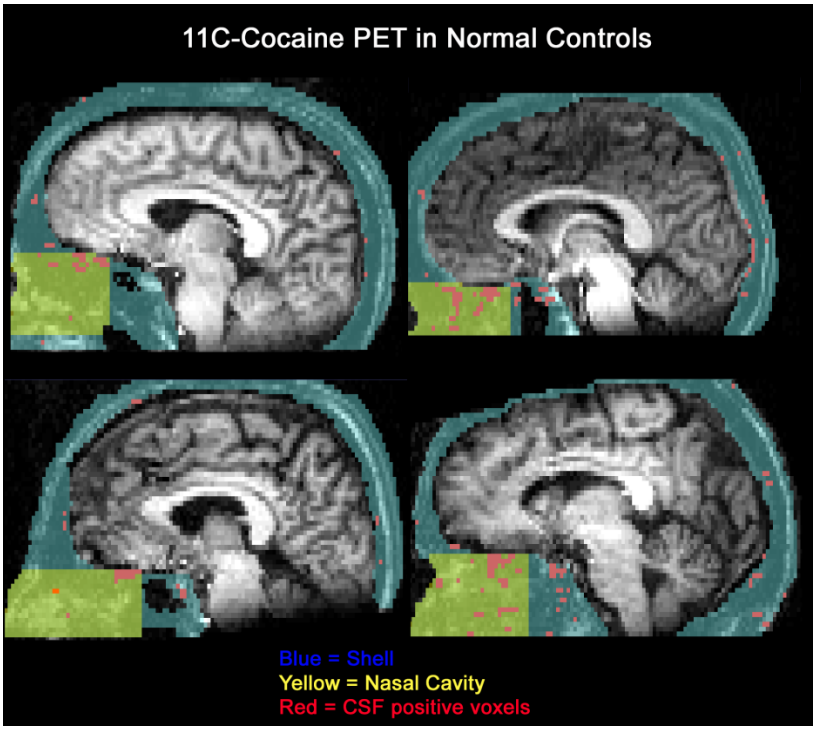
Supplemental Table 1: Partial volume corrections for tracer concentrations in Table 1

SUV (35-80)	S. turbinate	M. turbinate	Eye	Muscle	Shell
	1.26 (.24)	1.12 (.23) *	.71 (.58) *	.83 (.50) *	1.06 (.11) *

Data show Mean SUV 35-80min (SD)
* = different from superior turbinate, Wilcoxon Signed Rank Test p<.01

Dynamic PET studies of 40 min duration were carried out with a CTI 931 tomograph after injection of 6–8 mCi of ^{11}C-cocaine. Prior work has shown that there is rapid clearance and weak cortical binding of the tracer. We observed there was no nasal turbinate binding of the tracer in the 4 subjects studied.
The correlation between the ventricle sample ("peeled" 2 voxels around the ventricular margins) and all shell voxels was conducted as described in the text. To avoid partial volume errors, this procedure requires a relatively large ventricle to obtain a CSF sample. The study was limited to the older subjects who typically have larger ventricles.

1. Volkow ND, Wang G, Fischman MW, Foltin R, Fowler JS, Franceschi D, Franceschi M, Logan J, Gatley SJ,W ong C, Ding YS, Hitzemann R, Pappas N (2000) Effects of route of administration on cocaine induced dopamine transporter blockade in the human brain. Life Sci 67: 1507-1515.



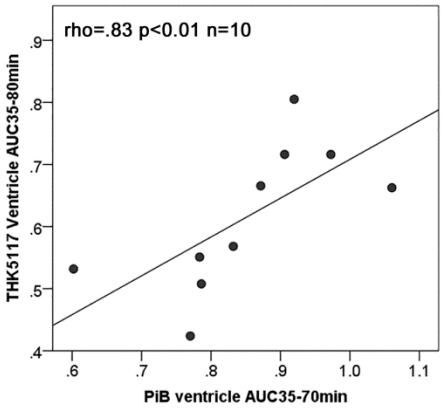
Supplemental Fig. 2 Voxels whose correlations exceeded r=.95 were considered CSF positive and are mapped in red below. Within the blue shell region, a nasal cavity region was defined in yellow. As observed with the THK5117 tau tracer, the highest density of presumed CSF positive sites is in the superior and middle turbinate regions.

Supplemental Video 1 Normal Subject Clearance

The ventricular CSF correlated nasal turbinate voxels are well seen in the video which visualizes the extra-cranial CSF transit over 9 min. Video 1 is a normal control subject demonstrating the transit of CSF correlated turbinate voxels from superior to inferior levels. Significant correlations first appear 3min post injection, at the superior turbinate and peri-dural areas and later are found more diffusely in the middle and inferior turbinates.

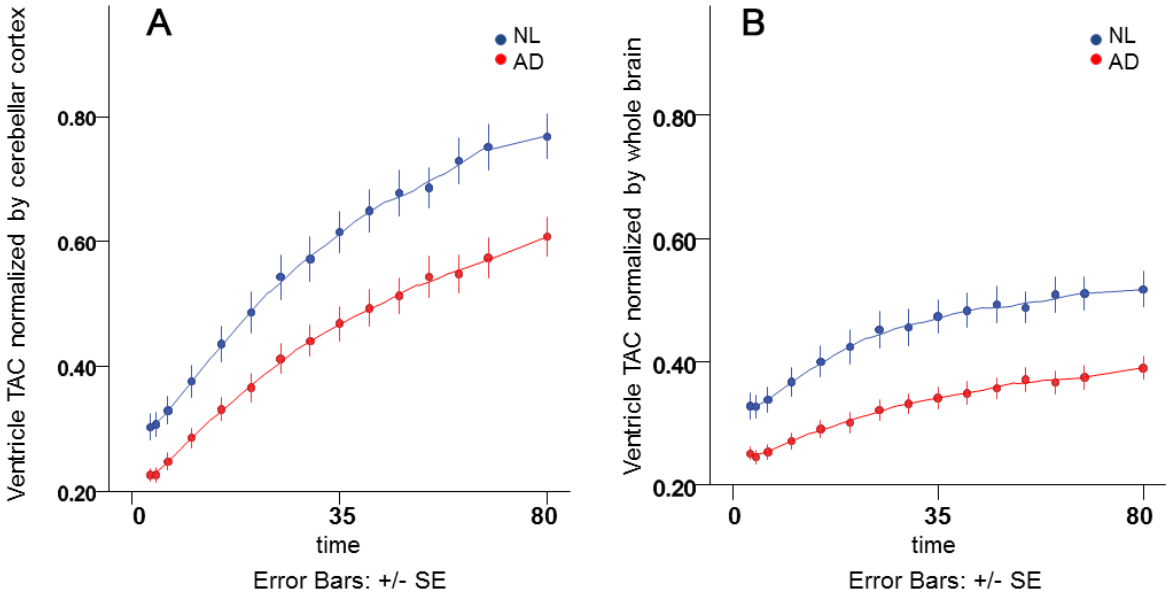
The video uses progressive 1 min temporal offsets for the correlations between the ventricle TAC and the TAC for individual shell voxels to demonstrate the anatomical trajectory of highly correlated CSF voxels. This was done by offsetting in 1 min increments the shell TAC and recomputing the correlation maps. With the ventricular TAC fixed at 3min post-injection, for example for 1 min delay, the shell TAC would start at 4min post-injection. For data delayed by 2 min, shell voxels acquired after 5min were aligned with the 3 min ventricular TAC, etc. We visualized for 9 minutes of offset the spatio-temporal trajectory of the CSF signal through the shell.

The relationship between the ventricular clearance of THK5117 and PiB



Supplemental Fig.3. Demonstrates the relationship between the ventricular clearance of THK5117 and PiB on the same subjects. For 10 subjects with both THK5117 and PiB scans we examined the correlation between the ventricular AUC35-80min. These data (rho=.83, p<.01) highlight the excellent precision of the ventricular CSF clearance measure.

The relationship between tau binding and CSF clearance.



Supplemental Fig.4. Compared with NL, AD subjects show lower ventricular $AUC_{35\text{-}80min}$ with both (A) cerebellar gray matter normalization (p=.01) and (B) total brain parenchyma normalization (p<.01).These data suggest large between group clearance differences with relatively smaller differential contributions from overall tracer retention.

Simulating cerebral blood flow (CBF) effects on the area under curve. One possible explanation for regional differences in area under the curve (AUC) is the CBF. To estimate the effect of regional perfusion rate *F* on AUC, representative datasets were simulated for a wide range of *F*. The simulation was governed by the kinetic model of a diffusible tracer in which the relation between the arterial input function c_a (t) and the tissue response function c (t) is given by:

$$c'(t) = F\{c_a(t) - c(t)\} \qquad \text{Eq. 1}$$

where prime denotes the time derivative. The analytic solution of Eq.1 is:

$$c(t) = Fe^{-Ft}\int_0^t c_a(u)e^{Fu}\,du \qquad \text{Eq. 2}$$

The arterial input was generated as the average of values extracted from all 15 patients after aligning the peaks.

Fig. A

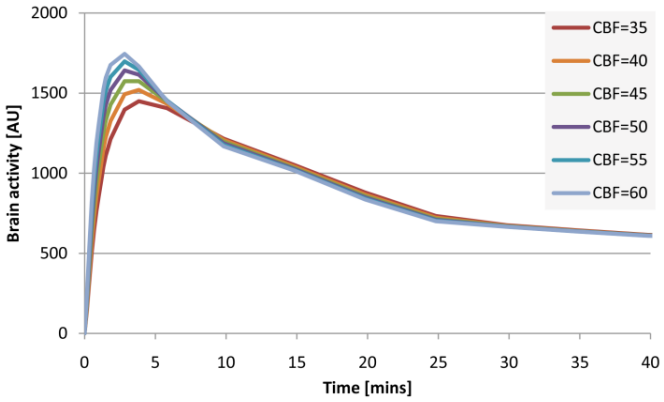
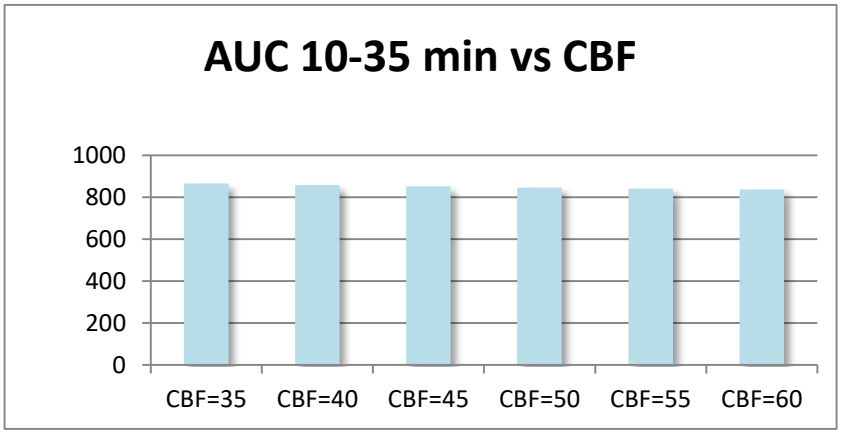


Fig. B



Supplemental Fig.5. A-B. **5A** shows the tissue activity curves for *F* varying in the range 35-60 ml/100g/min. **5B.** shows the corresponding distribution of AUC for the time period 10-35 min after injection, demonstrating negligible effect of F. These data show that the AUC were not affected by CBF over the time ranges studied.